INTERNATIONAL RESEARCH JOURNAL OF PHARMACY

www.irjponline.com

ISSN 2230 – 8407

Research Article

REPURPOSING DIABETES DRUGS FOR NEURODEGENERATIVE DISEASES: ANTI-DIABETIC DRUG REPOSITION

Mrugank Parmar [1], Shital Panchal [2]*

[1]PhD Research Scholar, Department of Pharmacology, Institute of Pharmacy, Nirma University, Ahmedabad - 382481, Gujarat, India

[2]Assistant Professor, Department of Pharmacology, Institute of Pharmacy, Nirma University, Ahmedabad - 382481, Gujarat, India

*Corresponding Author Email: Shital.Panchal@nirmauni.ac.in

Article Received on: 25/09/18 Approved for publication: 20/11/18

DOI: 10.7897/2230-8407.0912297

ABSTRACT

This study was aimed to find drug-repurposing opportunity of anti-diabetic drugs for treatment of neurodegenerative diseases using pharmacovigilance approach. We have retrieved the source data from United States FDA Adverse Event Reporting System for the last 15 years covering duration from 2004 to 2018. Medical dictionary for Regulatory Activities, version 19.1 was used to decode the relevant preferred terms for reported indications and side-effects. We have targeted reposition of anti-diabetic drugs for neurodegenerative disease. A primary target was set to identify anti-diabetic drug, which has therapeutic or prophylactic effect for neurodegenerative disease. Molecular mechanism of drugs and phenotypic characteristic of reported side-effects were compared with 'very common' side-effects of approved drugs for treatment of 'neurodegenerative disease'. Statistical analysis includes quantitative methods to calculate proportional reporting ratio for confirmed signal. Signals calculated with proportional reporting ratio value more than two, were only considered as positive result outcome. Through our systematic review of safety data, we have identified rosiglitazone, insulin (intranasal administration) and exenatide as convincing molecules for them reposition to treat neurodegenerative disease as novel therapeutic indication. Through this study, we have proposed to create a novel opportunity to find anti-diabetic drug that fully convinced for treatment of neurodegenerative disease. In future, well-designed, double-blind randomized controlled trials with large samples are required to conclude the efficacy of proposed reposition for anti-diabetic drugs.

Keywords: anti-diabetic, neurodegenerative disease, drug-reposition, pharmacovigilance, Alzheimer's Disease, Parkinson's Disease.

INTRODUCTION

"Neurodegenerative disease is an umbrella term for a range of conditions which primarily affect the neurons in the human brain. Neurons are the building blocks of the nervous system which includes the brain and spinal cord. Neurons normally don't reproduce or replace themselves, so when they become damaged or die they cannot be replaced by the body. Examples of neurodegenerative diseases include Parkinson's, Alzheimer's, and Huntington's disease. Neurodegenerative diseases are incurable and debilitating conditions that result in progressive degeneration and / or death of nerve cells. This causes problems with movement (called ataxias), or mental functioning (called dementias). Dementias are responsible for the greatest burden of neurodegenerative diseases, with Alzheimer's representing approximately 60-70% of dementia cases. Neurodegenerative disorders include brain ischemia, Alzheimer's disease (AD) and other dementias, Parkinson's disease (PD) and PD-related disorders, Prion disease, Motor neurone diseases (MND), Huntington's disease (HD), Spinocerebellar ataxia (SCA), Spinal muscular atrophy (SMA)"[1]. In this study, we have primarily focused on the treatment of brain ischemia, Alzheimer's disease and Parkinson's disease reported as most common neurodegenerative disorders. "Growth and development of neuroepidemiology in India during the last four decades has been documented highlighting the historical milestones. The prevalence rates of the spectrum of neurological disorders from different regions of the country ranged from 967-4,070 with a mean of 2394 per 100000 population, providing a rough estimate of over 30 million people with neurological disorders (excluding neuroinfections and traumatic injuries)."[2]

"AD and type 2 diabetes (T2DM) are two of the most common diseases of aging around the world. In the U.S., an estimated 5.4 million people of all ages have AD, and the risk of this disease increases with age. An estimated one in eight people aged older than 65 and one in two people 85 and older have AD. In the U.S., diabetes affects 25.8 million people of all ages (8.3% of the population), and the cumulative incidence of diabetes is 26.9% among people 65 and older. T2DM accounts for more than 90% of cases of diabetes in the U.S. and in many other developed countries. Given the frequency with which T2DM and AD occur, the notion that people with T2DM may be at increased risk for AD has large societal consequences, and understanding mechanistic links between these diseases is imperative for the development of effective AD prevention and treatment strategies."[3]

"One of the first reports to provide strong evidence that patients with T2DM are at a significantly increased risk of developing AD was the Rotterdam study".[4] "This prospective cohort study of 6,370 elderly subjects found that the presence of diabetes almost doubled the risk of developing AD. The risk of AD was even higher among patients treated with insulin, a group that likely had a longer history of diabetes and were refractory to oral agents. Several other large studies have also investigated the relationship between AD and elevated glucose levels, impaired glucose tolerance, and diabetes, and a systematic review and meta-analysis of these studies reported similar overall findings."[5]

"More recently, Crane et al. [6] showed that blood glucose level is positively associated with accelerated cognitive decline, even among individuals without clinical diabetes, after adjustment for multiple possible covariates including age, sex, blood pressure, smoking, and other determinants of macrovascular risk. Therefore, there is an increased risk of AD dementia with each serial increase in glucose level through the entire spectrum of possible glucose levels."

"Parkinson's disease is the second most common age-related neurodegenerative disorder after Alzheimer's disease. An estimated seven to 10 million people worldwide have Parkinson's disease. The prevalence of the disease ranges from 41 people per 100,000 in the fourth decade of life to more than 1,900 people per 100,000 among those who are 80 and older. The incidence of the disease, or the rate of newly diagnosed cases, generally increases with age, although it can stabilize in people who are older than 80. An estimated four percent of people with Parkinson's are diagnosed before age 50. Men are 1.5 times more likely to have Parkinson's than women. The disease affects patients' quality of life, making social interaction more difficult and worsening their financial condition, due to the medical expenses associated with the disease."[7]. "Current treatments are aimed at dopamine (DA) replacement and, although these treatments can initially be effective in relieving motor symptoms, over time complex motor fluctuations and dyskinesias can occur, which negatively impact patients' quality of life and mobility. Although more advanced therapies, including continuous intraduodenal infusion of levodopa, subcutaneous apomorphine infusions, and deep brain stimulation, have varying levels of success at minimising these motor complications, they ultimately have no effect on altering the progressive nature of the disease. Furthermore, over time, the involvement of nondopaminergic systems influences the onset of features such as depression, gait difficulties, and dementia, which are often refractory to treatment and have profound effects on patients' quality of life. Therefore, an urgent goal is to develop effective neuroprotective treatments that target pathways common to neurodegeneration and affect both dopaminergic and nondopaminergic systems and, therefore, that could slow the progression of the disease."[8]

"Ultimately, better understanding of the mechanisms underlying neurodegeneration should lead to better therapeutic options. As noted earlier, current therapies at best treat the symptoms of the disease but fail to slow disease progression. The goal of therapeutic development for neurodegenerative disorders is to develop drugs that slow down or stop the neurodegenerative process. So-called neuroprotective, or disease-modifying, therapies would not only treat the symptoms but slow the continued loss of neurons in disease. While such disease-modifying therapies may not be curative and restore those cells already lost by the time of diagnosis, such therapies would thus dramatically change the grim prognosis for most of these disorders."[9]

MATERIAL AND METHODS

Data collection from public database

Pharmacovigilance safety data were retrieved from United States FDA Adverse Event Reporting System (FAERS) for the last 15 years covering duration from 2004 to 2018. Medical dictionary for Regulatory Activities (MedDRA), Version 19.1 was used to decode the relevant MedDRA preferred terms for reported indications and side-effects. In our study, we targeted the drugs for repositioning, which are already in use for diabetes and drugs which are proved/analysed for their safe and effective use in human (clinical studies) or in animals (pre-clinical studies). A primary target was set to identify a drug, which may have at-least direct/indirect therapeutic or prophylactic effect for neurodegenerative disease therapy based on published literatures / research papers for their efficacy activity. Pharmacodynamic/molecular mechanism of drugs and phenotypic characteristic of reported side-effects were compared with 'very common' side-effects of drugs, which are approved for treatment of 'neurodegenerative disease'.

Study approach includes identifying the new indication of drugs for neurodegenerative disease based on their reported side-effects. If two drugs for the treatment of different disease are causing similar side-effects, then it indicate that there may be a possible correlation in between two drugs for some common mechanism of action and target receptor site. In other words, there is a phenotypic co-relation between side-effect and disease. Cases reported with only non-serious side-effects for at-least three times with same drug were considered for further analysis to identify a possible positive signal as per the study objective.

Isolation of serious and non-serious adverse drug reaction

Adverse drug reactions reported with any one or more of the following outcome "death; a life-threatening adverse event; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, a congenital anomaly/birth defect, important medical event terms (IME) or designated medical event (DME) term" were considered as serious adverse drug reaction and they were excluded from further analysis to meet the study objective.

Remaining all other adverse drug reactions were considered as non-serious adverse drug reactions and they were analysed further to meet the study objective.

Signal management to identify new indication for drug reposition

Signal management activity was performed for all the drug-event combination identified with possible positive signals based on their pharmacodynamic/molecular mechanism of drugs and phenotypic characteristic of reported event as non-serious side-effects. This activity was included the following steps in sequence;
"Signal detection by definition it is the process of looking for and/or identifying signals using data from published literatures and relevant authenticated source in support of published data."[10]

"Signal validation (and confirmation) by definition it is the process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis[10] of the signal. This evaluation was done into account the strength of the evidence, the clinical relevance and the previous awareness of the association." [10]

"Signal prioritisation, analysis and assessment by definition it is the process, continuously performed throughout signal management, which was aimed to identify those signals suggesting minimum or negligible safety concern with no potential important patients' or public health impact or which may not significantly affect the risk-benefit balance of the medicinal product and thus require urgent attention to meet the objective of this study to analyse them further for unapproved indication based on their reporting frequency and dechallenge / rechallenge outcome (if reported)." [10]

"Recommendation for further action as applicable, per the study objective"

Statistical analysis

Pharmacovigilance guideline[11] on the 'use of statistical signal detection methods in the EudraVigilance data analysis system' was used for statistical analysis in this study. This includes quantitative methods to calculate Proportional Reporting Ratio (PRR) for confirmed signal. Signals calculated with PRR value more than two, were only considered as positive result outcome.

RESULTS

Total 5,124,075 individual case safety reports (ICSRs) were reported for the duration from 2004 to 2018 to FDA Adverse Event Reporting System (FAERS) by various pharmaceutical organizations, physicians, patients or different health authorities. Of the total, 25,749 ICSRs were selected in which the patient was on the treatment for diabetes. Of the selected, 7639 ICSRs were reported with serious side-effects and hence as per the study objective they have been excluded from the further analysis. Remaining 18,110 ICSRs were reviewed for their reported drug therapy, medical/familial history and non-serious side-effects.

Most commonly reported non-serious side-effects were hypoglycaemia, unusual bleeding, angioedema, nausea, mild hypotension and fever with rosiglitazone; impaired glucose metabolism with insulin; dyskinesia (dose-limiting side effects occurs after few years of treatment), lightheadedness (dizziness), drowsiness (somnolence), anorexia with exenatide.

Comparative analysis of these non-serious side-effects and drugs was performed to understand their phenotypic characteristics and pharmacodynamic/molecular mechanism with respect to very common side-effects of drugs approved for treatment of 'neurodegenerative diseases' based on published literatures and standard reference book. Meta-analysis of published literatures and other authenticated sources suggest that, the side-effects reported with rosiglitazone (hypoglycaemia, unusual bleeding, angioedema, nausea, mild hypotension and fever); insulin (impaired glucose metabolism); and exenatide (dyskinesia as dose-limiting side effects occurs after few years of treatment, lightheadedness (dizziness), drowsiness (somnolence), anorexia, nausea, vomiting) may have phenotypic and pharmacodynamic/molecular mechanistic co-relation with 'very common' side-effects for the approved 'neurodegenerative diseases' drug therapy. Exhaustive review of published literature regarding clinical studies in various scientific databases (Embase, Medline and PubMed) also supports this analysis for treatment of 'neurodegenerative diseases' with use of rosiglitazone, insulin (intranasal administration) and exenatide. Following Table 1 summarize the proposed drugs for reposition for treatment of 'neurodegenerative diseases' based on its pharmacodynamic/molecular mechanism of action and reported non-serious side-effects.

Signal management activity was performed, supporting the confirmation of proposed drugs reposition for treatment of 'neurodegenerative diseases' as discussed in Table 1. PRR for the drugs and their reported non-serious events was calculated as summarized in below
Table 2. For all the proposed drugs reposition [Rosiglitazone, Insulin (Intranasal administration), and Exenatide], statistical analysis resulted PRR value more than two. Hence as per the guideline[10] use of statistical signal detection methods in the EudraVigilance data analysis system' all the proposed drugs should be considered for successful reposition through other confirmative pivotal clinical trial in future.

DISCUSSION

Rosiglitazone – Neuroprotective effects in brain ischaemia (stroke)

Brain ischemia is a leading cause of mortality worldwide and remains the primary cause of long-term neurological disability.[12]

The relative balance between plasma tissue plasminogen activator (tPA) and Plasminogen activator inhibitor (PAI)-1 activities is the important component that influence blood coagulation and the fibrinolytic system. tPA antigen and tPA/PAI-1 complex were known to be independently associated with stroke incidence, especially haemorrhagic stroke.[13] Patients with impaired fibrinolysis displayed decreased tPA and elevated PAI-1 activity. As a prominent acute phase reactant after cerebral ischemia, PAI-1 is always accompanied by a rapid inflammatory reaction. Elevated PAI-1 occurs secondly to inflammatory, which exacerbates cerebral injury.[14] Elevated PAI-1 level causes resistance to thrombolytics via platelet mediated mechanisms. Platelet-rich thrombosis has shown to be resistant to lysis by tPA. There is a steady decline in tPA activity together with an increased PAI-1 activity in chronic stage after stroke.[15] In the later stages, following cerebral thrombosis, the activity of plasma tPA and PAI-1 changed inversely especially plasma PAI-1 activity which significantly increased may be associated with a rebound hypercoagulable state and is therefore a potential cause of recurrent ischemic stroke. In summary, all these clinical studies shed light into the detrimental role of PAI-1 in the whole process of stroke.[16] In one case control study design, it was concluded that, high PAI-1 level was found more frequent in ischemic stroke subjects.[17]

Together with the recent observation that the activators of PPAR-γ a ligand reduces the incidence of stroke in patients with type 2 diabetes, this review supports the concept that rosiglitazone is effective drug against ischemic injury.[18]

Of the two FDA-approved thiazolidinediones, pioglitazone is known to cross BBB more efficiently than rosiglitazone, but the affinity of pioglitazone to PPAR is 10 times lower (Kd of 400 nM) than for rosiglitazone (Kd of 40 nM).[19,20] In addition to stimulating PPAR-γ, pioglitazone also functions as a partial agonist of PPAR-α, whereas rosiglitazone functions as a pure PPAR-γ agonist.[21]

Intranasal insulin in Alzheimer's disease

Alzheimer's disease is currently ranked as the sixth leading cause of death in the United States, but recent estimates indicate that the disorder may rank third, just behind heart disease and cancer, as a cause of death for older people. Alzheimer's is the most common cause of dementia among older adults. Alzheimer's disease and other forms of dementia are a growing public health problem among the elderly in developing countries, whose aging population is increasing rapidly. It is estimated that by the year 2020, approximately 70% of the world's population aged 60 and above will be living in developing countries, with 14.2% in India.[22]

National Institute of Health [23,24] has selected administration of intranasal insulin in AD patients which enables insulin to directly access the brain. This therapeutic strategy has received funding as part of the National Alzheimer's Plan in the US.

Table 1: Reported side-effects, proposed novel therapeutic indication and mechanism of action

Drug for reposition	Approved indication	New proposed indication	Phenotypic side-effects reported with drug for reposition	Pathophysiology of disease for 'new proposed indication'	Mechanism of action for new proposed indication concerning 'neurodegenerative diseases'
Rosiglitazone	Anti-diabetic (PPAR-γ agonist)	Neuroprotective effects in brain ischaemia (stroke)	Hypoglycaemia, unusual bleeding, angioedema, nausea, mild hypotension and fever [these are common side effect with alteplase – tissue Plasminogen Activator (tPA), and fibrinolytic drug]	Brain ischemia, also known as cerebral ischemia or cerebrovascular ischemia, occurs when there is an insufficient amount of blood flow to the brain. Brain ischemia can be further subdivided, into thrombotic, embolic, and hypoperfusion. Thrombotic and embolic are generally focal or multifocal in nature while hypoperfusion affects the brain globally. Focal brain ischemia occurs when a blood clot has occluded a cerebral vessel. Focal brain ischemia reduces blood flow to a specific brain region, increasing the risk of cell death to that particular area. It can be either caused by thrombosis or embolism. Astrocyte over-activation as well as extensive loss of neurons in the ischemic brain are the characteristic pathological features of ischemia stroke.	Rosiglitazone cause suppression of Plasminogen Activator Inhibitor-1 and may acts as fibrinolytic agent
Insulin (Intranasal administration)	The main indication of insulin is type I diabetes mellitus, diabetes mellitus of the pregnant women, diabetic ketoacetosis. It can be used, often in combination with other, anti-diabetic drugs for the treatment certain noninsulin-dependent diabetes	Alzheimer's Disease	Impaired glucose metabolism	Insulin resistance and downstream abnormalities in the insulin pathway is present in the patient with AD and contribute to the development of cognitive dysfunction	Intranasal insulin delivery bypasses the blood-brain barrier (BBB) and is rapidly delivered into the CSF compartment within 30–40 min following intranasal application
Exenatide	Anti-diabetic (GLP-1 agonist)	Parkinson's Disease	Dyskinesia (dose-limiting side effects occurs after few years of treatment), nausea, vomiting, lightheadedness (dizziness), drowsiness (somnolence), anorexia [these are	The main pathological characteristics of PD is cell death in the brain's basal ganglia and the presence of Lewy bodies (accumulations of the protein α-synuclein) The concentration of dopamine in the basal	Stimulation of Glucagon like peptide 1 (GLP-1) receptor leads to an increase in intracellular cAMP, activating protein kinase A (PKA), and phosphoinositide 3-kinase (PI3K) It further activates a variety of downstream

Drug for reposition	Approved indication	New proposed indication	Phenotypic side-effects reported with drug for reposition	Pathophysiology of disease for 'new proposed indication'	Mechanism of action for new proposed indication concerning 'neurodegenerative diseases'
			common side effect with levodopa]	ganglia of the brain is reduced in parkinsonism The net effect of dopamine depletion is to produce hypokinesia, an overall reduction in motor output.	signalling pathways that can be simplified into 2 branches: MAPK (mitogen associated protein kinase) and protein kinase B (AKT) pathways which can modulate intracellular events such as; - activation of calcium channels, enhancing protein synthesis, cellular proliferation and mitochondrial biogenesis, - While inducing inhibition of apoptosis, inflammation and protein aggregation – promoting cell survival and cause neuroprotection

PPAR - Peroxisome proliferator-activated receptors; GLP - Glucagon-like peptide-1

Table 2: Statistical signal analysis

Proposed drug for reposition	Reported events with proposed drug for reposition			Other medicinal products			Proportional reporting ratio
	Non-serious events Selected for 'neurodegenerative diseases' treatment	Other events	A+B	Non-serious events	Other events	C+D	
	A	B		C	D		
Rosiglitazone	87	212	299	98	835	933	2.77
Insulin (Intranasal administration)	54	152	206	79	684	763	2.53
Exenatide	56	114	170	67	436	503	2.47

A = number of individual cases with the suspect medicinal product P involving an adverse event R.
B = number of individual cases related to the suspect medicinal product P, involving any other adverse event except R.
C = number of individual cases involving event R in relation to any other medicinal products but P.
D = number of individual cases involving any other adverse events except R and any other medicinal products except P.
PRR = (A/(A+B))/(C/(C+D))

Results of published pilot studies for the administration of intranasal insulin in mild cognitive impairment (MCI) and AD patients have encouraged us for further research during this study. Of these all published studies, the most positive result was published in one double blind, randomized trial of 104 older adults with MCI or AD who received placebo, low-dose (20 IU), or high-dose (40 IU) intranasal insulin for four months [25]. In this study, as compared with placebo, participants who received either dose of insulin demonstrated significant improvements in memory as assessed by the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) and the Alzheimer's Disease Cooperative Study (ADCS) activities of daily living scales. These benefits of intranasal insulin were apparent not only at the end of the treatment period but also two months after treatment cessation, suggesting that intranasal insulin has long lasting effects on central nervous system (CNS) functioning.

Studies which compared results of primary outcomes between intranasal insulin and placebo showed noticeable improvement in memory and other brain cognitive function in the group treated by intranasal insulin. Other studies confirmed the modulation of intranasal insulin affected by ApoE ε4. ApoE ε4 is known risk factor for AD. It was shown in two studies [26,27] that AD patients who are not carriers of this genetic variant benefited more from the intranasal insulin treatment. The therapeutic efficacy of intranasal insulin has now been confirmed by a number of independent studies.[28]

Intravenous application of insulin is a highly invasive technique that leads to hypoglycemia, which itself has detrimental effects on brain function. Intranasal administration of insulin directly enters the brain, bypasses the blood-brain barrier (BBB) [29], and can be biologically detected in relevant concentrations in the cerebrospinal fluid (CSF) within 30–40 min following intranasal application [30]. with minimum effective doses that do not produce changes in peripheral blood levels of insulin and glucose. [31]

Exenatide in Parkinson's disease

Parkinson's disease is recognized as the second most common neurodegenerative disorder after Alzheimer's dis- ease and affects 1% of the population worldwide after the age of 65 years.[32] It is caused by the loss of dopamine-producing nerve cells in the part of the brain called the substantia nigra. Dopamine functions as a neurotransmitter and plays a key role in motor control. It is not known what causes the loss of these dopamine-producing nerve cells.

At present, there are no effective disease modifying or neuroprotective interventions: current therapies for PD treat the symptoms only. Available therapies include levodopa which is converted in the brain (as well as in the periphery) to dopamine, and dopamine receptor agonists that stimulate dopamine receptors.

Typically, PD is defined pathologically by prominent dopaminergic neuron loss and the presence of Lewy bodies containing α-synuclein in the brain. It is increasingly recognised that the neurodegenerative process in PD is complex and multifactorial, and is also likely to involve mitochondrial dysfunction and oxidative stress [33], inflammation [34], blood-brain barrier dysfunction [35], and neurovascular changes [36]. Such factors are likely to have treatment and prognostic implications. Vascular comorbidity (including prior stroke, TIA or more than two vascular risk factors), for instance, has recently been found to be significantly associated with cognitive and gait impairment in early PD.[37]

The incretin hormone glucagon-like peptide 1 (GLP-1) is best known for its effects on glucose homeostasis and facilitation of insulin signalling and, as such, agents that activate the GLP-1 receptor (GLP-1R), such as GLP-1 analogues or dipeptidyl peptidase 4 (DPP-IV) inhibitors, have been developed for use in the treatment of type 2 diabetes mellitus (T2DM). Accumulating evidence suggests that these GLP-1 analogues exert several extrapancreatic effects independent of glucose homeostasis and can cross the blood–brain barrier (BBB) to influence several cellular pathways, such as neuroinflammation, mitochondrial function, and cellular proliferation, within the CNS. Furthermore, a growing number of studies have demonstrated neuroprotective effects of GLP-1 R stimulation in models of PD, resulting in improvements in motor and non-motor deficits.[38]

Recent advances in understanding of the neuroprotective effects of incretin-based therapies, including GLP-1 receptor agonists, mean that there is considerable interest in their potential utility as repurposed treatments for several neurodegenerative disorders, including PD. People with PD treated with exenatide in an open-label clinical trial showed clinical benefit [39], with subsequent evidence of significant improvement in motor features 12 months after stopping exenatide [40]. Similarly, a recent double-blind clinical trial of people with PD found that those treated with exenatide showed improved motor features 60 weeks after coming off the medication, while motor features for those on placebo had worsened [41]. In this regard at 60 weeks, those on exenatide presented with a 1.0 point improvement in their off-medication scores on part 3 of the MDS-UPDRS as compared to those on placebo that worsened by 2.1 points over the same duration (to provide an adjusted mean difference of −3.5 points).

CONCLUSION

The neurodegenerative diseases are incurable, and significantly affect the patients' overall quality of life. Through this study, we have created an opportunity to find a drug that can fully revert the mechanisms of neurodegeneration. In future, well-designed, double-blind randomized controlled trials with large samples are required to assess the efficacy of proposed drugs for reposition.

Through this study, we have also proposed novel method for drug reposition and drug development using pharmacovigilance data which shall be more feasible and less time-consuming as compared with the study of compound chemical structure and other pharmacokinetic-pharmacodynamic studies. Though at present there is less awareness for drug-repositioning through pharmacovigilance method in research industry, now a day's innovator pharmaceutical organizations have started to establish a separate "Indication Discovery Unit" for long term benefit in terms of patent retention for their new chemical entity. On platform based analysis, these organizations have successfully launched their multiple approved molecules for unintended indications through a path of drug-repositioning and they have got the health authorities approvals with minimum cost of drug development for an orphan disease. This method may also enhance the fiscal growth of the organization globally and could help to keep their intellectual property rights with minimum investment. Evidently, continuous research on drug reposition through other publicly available large database may indeed provide a better treatment option for non-curative or an orphan disease..

ACKNOWLEDGMENTS

We wish to acknowledge the Institute of Pharmacy, Nirma University, located at Ahmedabad, Gujarat, India for offering us all the required support to complete the investigation for this study.

REFERENCES

1. JPND research. EU Joint Programme - Neurodegenerative Diseases Research. Available at http://www.neurodegenerationresearch.eu/ Accessed on 20 Sep 2018
2. Gourie-Devi M. Epidemiology of neurological disorders in India: review of background, prevalence and incidence of epilepsy, stroke, Parkinson's disease and tremors. Neurol India 2014;62:588–98.
3. Yarchoan M, Arnold SE. Repurposing diabetes drugs for brain insulin resistance in Alzheimer disease. Diabetes. 2014 Jul;63(7):2253-61.
4. Hofman A, Ott A, Breteler MM, et al. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. Lancet 1997;349:151–54
5. Kloppenborg RP, van den Berg E, Kappelle LJ, Biessels GJ. Diabetes and other vascular risk factors for dementia: which factor matters most? A systematic review. Eur J Pharmacol 2008;585:97–108.
6. Crane PK, Walker R, Hubbard RA, et al. Glucose levels and risk of dementia. N Engl J Med 2013;369:540–48
7. Parkinson's News Today. Parkinson's Disease Statistics. Available at https://parkinsonsnewstoday.com/parkinsons-disease-statistics/ Accessed on 20 Sep 2018
8. Athauda, D., Foltynie, T.,The glucagon-like peptide 1 (GLP) receptor as a therapeutic target in Parkinson's disease: mechanisms of action, Drug Discovery Today (2016), http://dx.doi.org/10.1016/j.drudis.2016.01.013 Accessed on 20 Sep 2018
9. Yacoubian, T.A. (2017). Neurodegenerative Disorders. 1-16. 10.1016/B978-0-12-802810-0.00001-5. Accessed on 20 Sep 2018.
10. European Medicines Agency, Heads of Medicines Agencies. Guideline on good pharmacovigilance practices (GVP): Module IX Signal management. 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129138.pdf. Accessed on 20 Sep 2018.
11. EudraVigilance Expert Working Group. The use of statistical signal detection methods in the EudraVigilance data analysis system. London, 16 November 2006. Doc. Ref. EMEA/106464/2006
12. Strong K, Mathers C, Bonita R. Preventing stroke: saving lives around the world. Lancet Neurol. 2007 Feb;6(2):182-7.
13. Johansson L, Jansson JH, Boman K, Nilsson TK, Stegmayr B, Hallmans G. Tissue plasminogen activator, plasminogen activator inhibitor-1, and tissue plasminogen activator/plasminogen activator inhibitor-1 complex as risk factors for the development of a first stroke. Stroke. 2000 Jan;31(1):26-32.
14. Kim JW, Lee SH, Ko HM, Kwon KJ, Cho KS, Choi CS et al. Biphasic regulation of tissue plasminogen activator activity in ischemic rat brain and in cultured neural cells: essential role of astrocyte-derived plasminogen activator inhibitor-1. Neurochem Int. 2011 Feb;58(3):423-33.

15. Zhuang P, Wo D, Xu ZG, Wei W, Mao HM. Dynamic changes in plasma tissue plasminogen activator, plasminogen activator inhibitor-1 and beta-thromboglobulin content in ischemic stroke. J Clin Neurosci. 2015 Jul;22(7):1123-7.
16. Chen R, Yan J, Liu P, Wang Z, Wang C. Plasminogen activator inhibitor links obesity and thrombotic cerebrovascular diseases: The roles of PAI-1 and obesity on stroke. Metab Brain Dis. 2017 Jun;32(3):667-73.
17. Surjawan, Y., Setiabudy, R., Suryaatmadja, M., Ranakusuma, T. The association of plasminogen activator inhibitor-1 level with ischemic stroke (preliminary study). Med J Indones. 2010 Aug 1;19(3):158-63.
18. Culman J, Zhao Y, Gohlke P, Herdegen T. PPAR-gamma: therapeutic target for ischemic stroke. Trends Pharmacol Sci. 2007 May;28(5):244-9.
19. Berger J, Moller DE. The mechanisms of action of PPARs. Annu Rev Med. 2002;53:409-35.
20. Young PW, Buckle DR, Cantello BC, Chapman H, Clapham JC, Coyle PJ et. al. Identification of high-affinity binding sites for the insulin sensitizer rosiglitazone (BRL-49653) in rodent and human adipocytes using a radioiodinated ligand for peroxisomal proliferator-activated receptor gamma. J Pharmacol Exp Ther. 1998 Feb;284(2):751-9.
21. Sakamoto J, Kimura H, Moriyama S, Odaka H, Momose Y, Sugiyama Y et. al. Activation of human peroxisome proliferator-activated receptor (PPAR) subtypes by pioglitazone. Biochem Biophys Res Commun. 2000 Nov 30;278(3):704-11.
22. World Health Organization. Fact Sheet No 135. Geneva: World Health Organization; 1998. Population Ageing – A Public Health Challenge
23. Thorne RG, Pronk GJ, Padmanabhan V, Frey WH 2nd. Deliveryof insulin-like growth factor-I to the rat brain and spinal cordalong olfactory and trigeminal pathways following intranasal administration. Neuroscience. 2004;127(2):481–96.
24. Born J, Lange T, Kern W, McGregor GP, Bickel U, Fehm HL.Sniffing neuropeptides: a transnasal approach to the human brain.Nat Neurosci. 2002;5(6):514–6.
25. Craft S, Baker LD, Montine TJ, et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Arch Neurol. 2012;69:29–38
26. RReger MA, Watson G, and Green PS et al. Intranasal insulin administration dose-dependently modulates verbal memory and plasma amyloid-βin memory-impaired older adults. J Alzheimers Dis 2008;13:323-31.
27. Claxton A, Baker LD, and Wilkinson CW et al. Sex and ApoE genotype differences in treatment response to two doses of intranasal insulin in adults with mild cognitive impairment or Alzheimer's disease. J Alzheimers Dis 2013;35:789-97.
28. Schiöth HB, Frey WH, Brooks SJ, Benedict C. Insulin to treat Alzheimer's disease: just follow your nose? Expert Rev Clin Pharmacol. 2012 Jan;5(1):17-20.
29. Baura GD, Foster DM, Porte D Jr, Kahn SE, Bergman RN, CobelliC, et al. Saturable transport of insulin from plasma into thecentral nervous system of dogs in vivo. A mechanism for regulatedinsulin delivery to the brain. J Clin Invest.1993;92(4):1824–30.
30. Hallschmid M, Schultes B, Marshall L, Molle M, Kern W,Bredthauer J, et al. Transcortical direct current potential shiftreflects immediate signaling of systemic insulin to the humanbrain. Diabetes. 2004;53(9):2202–8.
31. Born J, Lange T, Kern W, McGregor GP, Bickel U, Fehm HL.Sniffing neuropeptides: a transnasal approach to the human brain.Nat Neurosci. 2002;5(6):514–6.
32. Tanner CM, Goldman SM. Epidemiology of Parkinson's disease. Neurol Clin. 1996 May;14(2):317-35.
33. Abou-Sleiman PM, Muqit MM, Wood NW. Expanding insights of mitochondrial dysfunction in Parkinson's disease. Nature Reviews. Neuroscience 2006;7(3):207-19.
34. Collins LM, Toulouse A, Connor TJ, Nolan YM. Contributions of central and systemic inflammation to the pathophysiology of Parkinson's disease. Neuropharmacology 2012;62(7):2154-68.
35. Gray MT, Woulfe JM. Striatal blood-brain barrier permeability in Parkinson's disease. Journal of Cerebral Blood Flow & Metabolism 2015;35(5):747-50.
36. Al-Bachari S, Vidyasagar R, Emsley HC, Parkes LM. Structural and physiological neurovascular changes in idiopathic Parkinson's disease and its clinical phenotype. Journal of Cerebal Blood Flow & Metabolism 2017;37(10):3409-21.
37. Malek N, Lawton MA, Swallow DM, Grosset KA, Marrinan SL, Bajaj N, et al. Vascular disease and vascular risk factors in relation to motor features and cognition in early Parkinson's disease. Movement Disorders 2016;31(10):1518-26.
38. Athauda D, Foltynie T. The glucagon-like peptide 1 (GLP) receptor as a therapeutic target in Parkinson's disease: mechanisms of action. Drug Discov Today. 2016 May;21(5):802-18.
39. Aviles-Olmos I, Dickson J, Kefalopoulou Z, Djamshidian A, Ell P, Soderlund T, et al. Exenatide and the treatment of patients with Parkinson's disease. Journal of Clinical Investigation 2013;123(6):2730-6.
40. Aviles-Olmos I, Dickson J, Kefalopoulou Z, Djamshidian A, Kahan J, Ell P, et al. Motor and cognitive advantages persist 12 months after exenatide exposure in Parkinson's disease. Journal of Parkinson's Disease 2014;4(3):337-44.
41. Athauda D, Maclagan K, Skene SS, Bajwa-Joseph M, Letchford D, Chowdhury K, et al. Exenatide once weekly versus placebo in Parkinson's disease:a randomised, double-blind, placebo-controlled trial. Lancet 2017;390:1664-75.
42. Vexler ZS, Tang XN, Yenari MA. Inflammation in adult and neonatal stroke. Clin Neurosci Res. 2006;6:293–313.

Cite this article as:

Mrugank Parmar and Shital Panchal. Repurposing diabetes drugs for neurodegenerative diseases: Anti-diabetic drug reposition. Int. Res. J. Pharm. 2018;9(12):81-87 http://dx.doi.org/10.7897/2230-8407.0912297

Source of support: Nil, Conflict of interest: None Declared